Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 15, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.05.059

Elevated Cardiac Troponin T Is Associated With Higher Mortality and Amputation Rates in Patients With Peripheral Arterial Disease

Birgit Linnemann, MD,*† Thilo Sutter,* Eva Herrmann, MD,‡ Sebastian Sixt, MD,* Aljoscha Rastan, MD,* Uwe Schwarzwaelder, MD,* Elias Noory, MD,* Karlheinz Buergelin, MD,* Ulrich Beschorner, MD,* Thomas Zeller, MD*

Bad Krozingen and Frankfurt/Main, Germany

Objectives The aim of the present study was to evaluate whether elevated cardiac troponin T (cTnT) was independently associated with an increased all-cause mortality or risk of cardiovascular events and amputation among patients with peripheral arterial disease (PAD).

Background PAD patients often have impaired renal function, and the blood concentration of cardiac troponin often increases with declining glomerular filtration rate.

Methods The cohort consisted of 1,041 consecutive PAD patients (653 males, 388 females, age 70.7 ± 10.8 years, Rutherford stages 2 to 5) undergoing endovascular peripheral revascularization.

Results At baseline, measurable cTnT levels (≥0.01 ng/ml) were detected in 21.3% of individuals. Compared with patients who had undetectable cTnT levels, those with cTnT levels ≥0.01 ng/ml had higher rates for mortality (31.7% vs. 3.9%, respectively; $p < 0.001$), myocardial infarction (4.1% vs. 1.1%, respectively; $p = 0.003$), and amputation (10.1% vs. 2.4%, respectively; $p < 0.001$) during a 1-year follow-up. In adjusted Cox regression models, cTnT levels ≥0.01 ng/ml were associated with increased total mortality (hazard ratio [HR]: 8.14; 95% confidence interval [CI]: 3.77 to 17.6; $p < 0.001$) and amputation rates (HR: 3.71; 95% CI: 1.33 to 10.3; $p = 0.012$).

Conclusions cTnT is frequently elevated in PAD patients and is associated with higher event rates in terms of total mortality and amputation. Even small cTnT elevations predict a markedly increased risk that is independent of an impaired renal function. (Troponin T as Risk Stratification Tool in Patients With Peripheral Arterial Occlusive Disease; NCT01087385) (J Am Coll Cardiol 2014;63:1529–38) © 2014 by the American College of Cardiology Foundation

Cardiac troponin T (cTnT) is a component of the contractile apparatus of cardiomyocytes and an established sensitive biomarker of myocardial cell injury. Therefore, testing for this biomarker is recommended for the diagnosis of myocardial infarction in the clinical setting of an acute coronary syndrome (ACS) (1). An elevated cTnT level is associated with an adverse outcome after ACS (2,3) in patients with chronic heart failure (4,5), acute pulmonary embolism (6), and end-stage renal disease (ESRD) (7,8) and in the general population (9–12). The clinical significance of detectable cTnT among patients with peripheral arterial occlusive disease (PAD) is unknown. Recently, some investigations have reported that elevated cTnT levels may also be of prognostic value in patients with acute limb ischemia (13,14). However, cardiac troponin levels often increase with a declining glomerular filtration rate, and many PAD patients have impaired renal function (15,16).

See page 1539

There is evidence that chronic kidney disease itself is associated with an increased cardiovascular mortality (17,18). Elevated cTnT levels are also associated with other vascular risk factors, such as age, male sex, and diabetes (9,19,20). This study was performed to define the distribution and determinants of measurable cTnT among symptomatic PAD patients and to explore its prognostic impact on mortality, amputation rates, and cardiovascular outcomes during follow-up.

From the *Department of Angiology, University Heart Center Bad Krozingen, Bad Krozingen, Germany; †Division of Vascular Medicine, Department of Internal Medicine, Goethe University Hospital Frankfurt/Main, Frankfurt/Main, Germany; and the ‡Institute of Biostatistics and Math, Modeling, Faculty of Medicine, Goethe University Hospital Frankfurt/Main, Frankfurt/Main, Germany. Dr. Herrmann is a consultant for Roche Pharma and Novartis Pharmaceuticals. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received January 10, 2013; revised manuscript received April 18, 2013, accepted May 5, 2013.

JACC Vol. 63, No. 15, 2014
April 22, 2014:1529–38

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
CHD = chronic heart disease
CKD = chronic kidney disease
CLI = critical limb ischemia
cTnT = cardiac troponin T
eGFR = estimated glomerular filtration rate
ESRD = end-stage renal disease
PAD = peripheral arterial disease

Methods

Study design and participants. This retrospective single-center study enrolled 1,065 consecutive symptomatic PAD patients at Rutherford stages 2 to 5 (Fontaine stages IIb to IV). Patients were admitted to our university teaching hospital between January 2007 and December 2007 for urgent or elective endovascular revascularization. The ankle-brachial index and diagnostic workup by a color-coded duplex scan were routinely used before angiography to confirm the diagnosis of PAD and to determine the therapeutic strategy. All patients were followed for a period of at least 12 months or until death. Most of the patients were regularly seen in the outpatient department for diagnostic follow-up and were asked to answer a standardized questionnaire. To obtain information about mortality and vascular morbidity, we reviewed medical records and contacted the patients and their general practitioners. Outcome data were available for 1,012 patients (95.0%) (Fig. 1). The protocol was approved by the local ethics committee and registered at ClinicalTrials.Gov (NCT01087385).

The exclusion criteria were all conditions that may acutely increase cTnT levels. Myocardial ischemia or clinical symptoms indicating unstable angina pectoris or ACS within the previous 14 days resulted in exclusion from analysis. Additional exclusion criteria were acute pulmonary embolism, aortic dissection, New York Heart Association functional class III or IV heart failure, cardiomyopathy, endocarditis/myocarditis, external electrical cardioversion for atrial fibrillation, and heart surgery within the previous 14 days. By contrast, chronic kidney disease (CKD) and impaired renal function were not exclusion criteria.

Laboratory assessment. Blood samples were collected upon hospital admission. cTnT was measured with the fourth-generation assay Elecsys troponin T using a Cobas 6000 e601 system (Roche Diagnostics, Mannheim, Germany) according to the recommendations of the manufacturer. The 99th percentile value for the reference population used by the manufacturer of the assay was 0.01 ng/ml, and the lowest level at which the coefficient of variation was <10% was 0.03 ng/ml (21). A cutoff value of 0.01 ng/ml, which corresponds to the 99th percentile of a reference population and the lowest level of detection, was chosen to define an elevated cTnT level (22). Measurement of cTnT was routinely performed in all PAD patients upon hospital admission. However, the cTnT values were missing for 7 patients, who were censored from further statistical analysis (Fig. 1).

In addition, laboratory testing included automated and standardized testing of serum creatinine levels. The estimated glomerular filtration rate (eGFR) was determined by the Cockcroft-Gault formula and classified using standards set forth by the National Kidney Foundation Disease Outcomes Quality Initiative (23). According to these standards, we defined an impaired renal function as an eGFR concentration of <60 ml/min.

Baseline characteristics, comorbidities, and medication. Assessment of atherosclerotic disease and cardiovascular risk

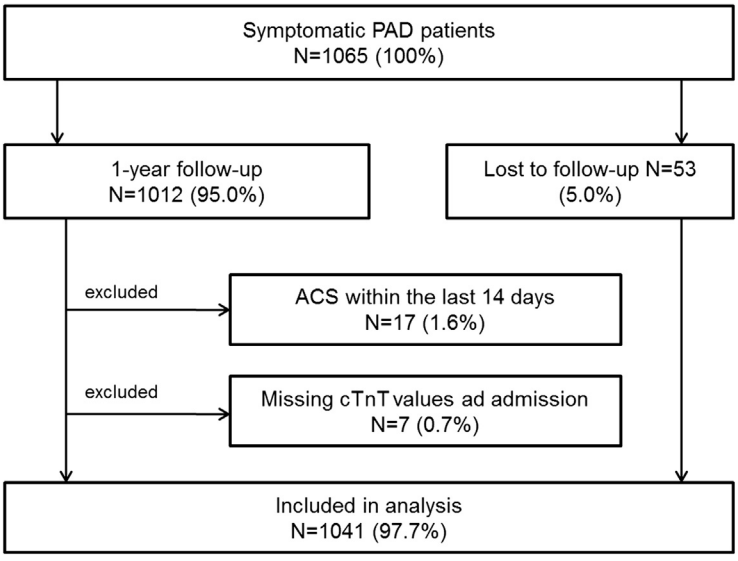

Figure 1 Study Design

ACS = acute coronary syndrome(s); cTnT = cardiac troponin T; PAD = peripheral arterial disease.

factors was based on clinical history, clinical examination, and laboratory test results. Patients were interviewed about a history of coronary heart disease, ischemic cerebral infarction or transient ischemic attack, and PAD. Patients' smoking status, classified as currently smoking versus never or previously smoked combined, was obtained using a standardized questionnaire. Diabetes mellitus was diagnosed in accordance with the World Health Organization classification (24). Arterial hypertension was defined by a systolic blood pressure of more than 140 mm Hg, a diastolic blood pressure of more than 90 mm Hg, or both on at least 2 occasions or by the use of antihypertensive drugs (25). Hypercholesterolemia was defined as a fasting cholesterol level exceeding 200 mg/dl, a low-density lipoprotein cholesterol level of at least 130 mg/dl, or both on at least 2 occasions or by the use of lipid-lowering drugs (26). Finally, patient medications were also recorded.

Clinical evaluation and ECG registration. Seventeen patients in the initial cohort had had an ACS within the previous 14 days before study entry and were censored from further statistical analysis (Fig. 1). There was no clinical evidence of myocardial ischemia among the remaining patients. We analyzed the patients' electrocardiograms (ECG), which were performed simultaneously with blood sampling at the time of admission to the hospital. According to the consensus document of the Joint European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), World Heart Federation (WHF) Task Force for the Redefinition of Myocardial Infarction (1), we registered ECG changes that might be indicative of acute myocardial ischemia, for example: 1) ST-segment elevation at the J-point in 2 contiguous leads with the cut-off points of $\geq$0.2 mV in men or $\geq$0.15 mV in women in leads V_2 to V_3 and/or $\geq$0.1 mV in other leads; 2) horizontal or down-sloping ST-segment depression of $\geq$0.05 mV and/or T-wave inversion of $\geq$0.1 mV in 2 contiguous leads; and 3) the presence of left bundle branch block.

Patient outcomes. Differences between outcomes after 12 months were determined for patients with elevated and those with normal cTnT concentrations. The primary outcomes examined in this analysis included total mortality and amputation. Secondary outcomes included myocardial infarction, ACS, and target limb revascularization. ACS was defined as a non–ST-segment and ST-segment myocardial infarction or unstable angina resulting in admission to the hospital. All reported events were confirmed by a review of medical records.

Statistical analysis. If not stated otherwise, the statistical analysis was performed using Statistical Package for Social Sciences (SPSS Statistics version 20.0, IBM, Chicago, Illinois). The baseline characteristics are reported as percentages for categorical variables and mean ± SD for continuous variables. We used the chi-square test in cross-tabulations and the Mann-Whitney *U* test to compare metric variables. Differences in outcomes were compared between patients with elevated and those with normal cTnT concentrations. Cox proportional hazards models were used to examine the relationship between the cTnT levels determined at baseline and the outcome events. In these models, the cTnT level was examined as a categorical variable. The Cox models sequentially added age, eGFR, and the presence or absence of current smoking, diabetes, and critical limb ischemia (CLI). Age and eGFR were modeled as continuous variables. The final model also excluded all patients with ECG changes conformable with acute myocardial ischemia, according to the latest consensus document of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction (1). All tests were 2-sided, and the criterion for statistical significance was a p value of $<$0.05.

Under conditions of competing risks, Cox regression models can produce misleading results, so a competing risk approach implemented in the software survival of R version 2.14.0 (R Development Team, R Foundation for Statistical Computing, Vienna, Austria) was used. We plotted the overall cumulative incidence of amputation outcomes and mortality (death before and after amputation) stratified by cTnT levels of $<$0.01 ng/ml and $\geq$0.01 ng/ml. Differences in curves were tested using the log-rank test. Furthermore, a reclassification analysis was performed using the Hmisc software package of R by Frank E. Harrell to quantify and compare the concordance of different predictors for mortality.

Results

Baseline characteristics of the study cohort. The clinical characteristics and demographic information available for the definitive study cohort of 1,041 patients are summarized in Table 1. The mean age of patients was 70.7 (±10.8) years; and 62.7% were males, 44.9% were known to have coronary artery disease (CAD), and 12.0% had a history of cerebral infarction.

Determinants of elevated troponin T. cTnT was detectable ($\geq$0.01 ng/ml) in 222 patients (21.3%). Patients with cTnT values $\geq$0.01 ng/ml were older, more likely to be male or diabetic, and less likely to have hypercholesterolemia or to be current smokers compared with patients with cTnT values $<$0.01 ng/ml. An elevated cTnT concentration was also associated with an impaired renal function (Fig. 2), cardio- and cerebrovascular comorbidities, and severe PAD. In patients with intermittent claudication (i.e., Rutherford stages 2 and 3), a cTnT of $\geq$0.01 ng/ml was present in 54 of 623 cases (8.7%) compared with 168 of 418 patients (40.2%) with CLI (i.e., Rutherford stages 4 and 5; $p < 0.001$). In addition, PAD was localized more distally among patients with a cTnT elevation. In 121 cases (54.5%), the revascularization procedure involved the tibial or peroneal arteries compared with 272 cases (33.2%) of patients with undetectable cTnT ($p < 0.001$) (Table 1).

One-year outcomes. During a 1-year follow-up, 106 patients died (9.7%). In 14 patients (1.4%), a major amputation was unavoidable, and 29 patients (2.9%) underwent minor amputation. The overall amputation rate was 4.1% (Table 2).

Table 1 Characteristics of the Study Sample by Baseline Troponin T Concentration

Parameter	Total Cohort (N = 1,041)	cTnT <0.01 ng/ml (n = 819)	cTnT ≥0.01 ng/ml (n = 222)	p Value
Demographics				
Age, yrs	70.7 ± 10.8	69.7 ± 10.8	74.5 ± 10.1	<0.001
Males	653 (62.7%)	498 (60.8%)	155 (69.8%)	0.015
Vascular risk factors and comorbidities				
Current smoking	251 (24.1%)	234 (28.6%)	17 (7.7%)	<0.001
Diabetes mellitus	424 (40.7%)	299 (36.5%)	125 (56.3%)	<0.001
Arterial hypertension	889 (85.4%)	690 (84.2%)	199 (89.6%)	0.044
Hypercholesterolemia	828 (79.5%)	662 (80.8%)	166 (74.8%)	0.049
Coronary artery disease	467 (44.9%)	333 (40.7%)	134 (60.4%)	<0.001
Prior cerebral infarction	125 (12.0%)	85 (10.4%)	40 (18.0%)	0.003
Prior peripheral vascular intervention	470 (45.1%)	378 (46.2%)	92 (41.4%)	0.224
Prior peripheral bypass surgery	87 (8.4%)	73 (8.9%)	14 (6.3%)	0.273
Prior amputation	82 (7.9%)	48 (5.9%)	34 (15.3%)	<0.001
Chronic kidney disease (stages 3 to 5)	400 (38.4%)	237 (28.9%)	163 (73.4%)	<0.001
End-stage renal failure	66 (6.3%)	5 (0.6%)	61 (27.5%)	<0.001
PAD characteristics				
Rutherford category 2	287 (27.6%)	259 (31.6%)	28 (12.6%)	<0.001
Rutherford category 3	336 (32.3%)	310 (37.9%)	26 (11.7%)	—
Rutherford category 4	128 (12.3%)	94 (11.5%)	34 (15.3%)	—
Rutherford category 5	290 (27.9%)	156 (19.0%)	134 (60.4%)	—
Revascularized arterial segments				
Iliac artery	224 (21.5%)	192 (23.4%)	32 (14.4%)	0.003
Femoropopliteal artery	773 (74.3%)	612 (74.7%)	161 (72.5%)	0.545
Tibial or peroneal artery	393 (37.8%)	272 (33.2%)	121 (54.5%)	<0.001
Endovascular revascularization procedures				
Occlusion/recanalization	547 (52.5%)	427 (52.1%)	120 (54.1%)	0.650
POBA	170 (16.3%)	122 (14.9%)	48 (78.4%)	0.019
Bare-metal stent	882 (84.7%)	700 (85.5%)	182 (82.0%)	0.207
Drug-eluting stent	182 (17.5%)	144 (17.6%)	38 (17.1%)	0.921
Mechanical atherectomy	97 (9.3%)	83 (10.1%)	14 (6.3%)	0.091
Mechanical thrombectomy	65 (6.2%)	50 (6.1%)	15 (6.8%)	0.754
Local thrombolysis	64 (6.1%)	54 (6.6%)	10 (4.5%)	0.344
Bypass surgery	20 (1.9%)	16 (2.0%)	4 (1.8%)	0.978
Medication at discharge				
Aspirin or other antiplatelet medication	997 (96.8%)	797 (97.4%)	200 (94.3%)	0.029
Vitamin K antagonists	212 (20.4%)	141 (17.2%)	71 (33.5%)	<0.001
Beta-blocker	611 (59.4%)	462 (56.5%)	149 (70.6%)	<0.001
ACE inhibitor or AT1 receptor antagonist	732 (70.3%)	581 (70.9%)	151 (68.0%)	0.408
Lipid-lowering drug	752 (72.2%)	631 (77.1%)	121 (57.1%)	<0.001

Values are n (%). p Values refer to comparisons between patients with and those without elevated troponin T.
ACE = angiotensin-converting enzyme; AT1 = angiotensin type-1; cTnT = cardiac troponin T; PAD = peripheral arterial disease; POBA = plain old balloon angioplasty.

Due to the progression of PAD, subsequent peripheral revascularization procedures were required, and target limb revascularization was performed in 24.3% of patients. Myocardial infarction occurred in 1.9% of patients during follow-up, and 4.6% of patients were hospitalized with an ACS.

Total mortality and amputation risk according to troponin T. Detectable cTnT levels ranged from 0.010 to 0.482 ng/ml. The distributions of cTnT by total mortality, cardiac events, and amputation are demonstrated in Figure 3. The mortality and amputation rates in patients with elevated cTnT (≥0.01 ng/ml) were increased compared with those with normal cTnT (Table 2), resulting in an unadjusted hazard ratio (HR) of 9.87 (95% confidence interval [CI]: 6.49 to 15.0) for total mortality and 4.92 (95% CI: 2.68 to 9.03) for amputation.

The cumulative incidence curves for amputation outcomes and mortality (death before and after amputation) stratified by cTnT <0.01 ng/ml and ≥0.01 ng/ml are demonstrated in Figure 4. Comparing 1-year outcomes between patients with cTnT values ≥0.01 ng/ml and those with <0.01 ng/ml, mortality risk was 32.9% vs. 4.0% (log-rank test, $p < 0.001$), respectively, and the risk of amputation was 9.9% vs. 2.4% (log-rank test, $p < 0.001$), respectively.

No differences were observed for the incidence of peripheral revascularization procedures. Regarding mortality, similar associations were observed in a subgroup

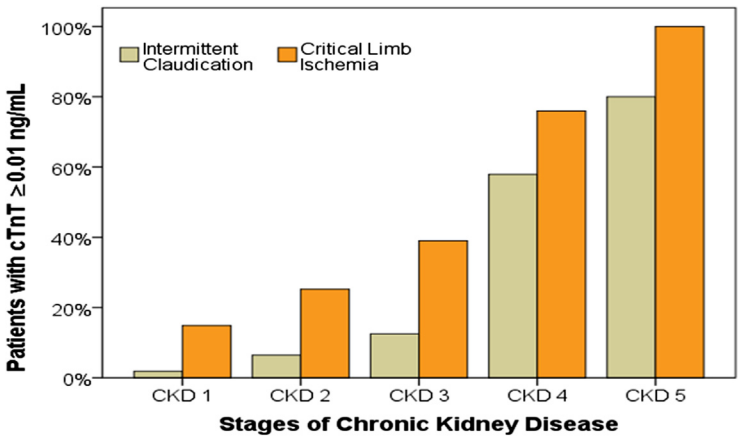

Figure 2 Prevalence of Elevated Cardiac Troponin T

The prevalence of elevated cardiac troponin T (cTnT ≥0.01 ng/ml) among patients with intermittent claudication or critical limb ischemia (CLI), according to chronic kidney disease (CKD) classification using the estimated glomerular filtration rate I: >90 ml/min; II: 60 to 89 ml/min; III: 30 to 59 ml/min; IV: 15 to 29 ml/min; V: <15 ml/min; or dialysis.

analysis of patients with CLI (HR: 9.51; 95% CI: 3.94 to 23.0) and patients with intermittent claudication (HR: 5.01; 95% CI: 3.08 to 8.17). A corresponding subgroup analysis for amputation was not meaningful because only 2 amputations were performed in the subgroup of patients with intermittent claudication.

After adjusting for age, eGFR and the presence or absence of current smoking, diabetes, and CLI (Model 2), the mortality risk in the total cohort remained increased, with cTnT ≥0.01 ng/ml (HR: 4.64; 95% CI: 2.82 to 7.64; $p < 0.001$). However, in multivariate analysis, the amputation risk was no longer significant (HR: 1.86; 95% CI: 0.92 to 3.74; $p = 0.083$) (Table 3).

The introduction of cTnT improved the prognostic discrimination for mortality outcomes. The addition of cTnT to Model 2 (c-statistic: 0.802 ± 0.039) offered moderate improvement (c-statistic with cTnT: 0.835 ± 0.036). Quantifying and comparing Harrell's concordance, cTnT led to an improvement of risk reclassification (U-statistic: 0.30 ± 0.06).

No patient at baseline included in this analysis had clinical symptoms of unstable angina. Patients with an ACS within the previous 14 days before blood sampling had been excluded from the analysis. However, the interpretation of ECGs performed upon admission to hospital revealed significant differences in the frequencies of ECG criteria conformable with acute myocardial ischemia among patients with and without elevated cTnT (Table 4). Repeating the analysis after exclusion of all patients with any ECG changes suggestive of acute myocardial ischemia (Model 3), the HRs (and corresponding 95% CIs) were 8.14 (95% CI: 3.77 to 17.6; $p < 0.001$) for total mortality and 3.71 (95% CI: 1.33 to 10.3; $p = 0.012$) for amputation.

Troponin T and myocardial infarction. During the 1-year follow-up, we registered a total of 20 myocardial infarctions (1.9%). Unadjusted analysis revealed a risk of myocardial infarction for patients with cTnT values ≥0.01 ng/ml (HR: 3.75; 95% CI: 1.55 to 9.05) (Table 2). After adjusting for age and eGFR, the association remained significant (HR: 3.40; 95% CI: 1.23 to 9.45; $p = 0.019$) (Model 1). In the final model after exclusion of all patients with ECG changes that might indicate acute myocardial ischemia (Model 3), these associations were no longer significant (HR: 3.44; 95% CI: 0.86 to 13.7; $p = 0.080$).

Table 2 1-Year Mortality Rates and Incidence of Primary and Secondary Outcomes According to Cardiac Troponin T at Baseline

Event	No. in Total Cohort (%) (N = 1,041)	No. of cTnT <0.01 ng/ml (%) (n = 819)	No. of cTnT ≥0.01 ng/ml (%) (n = 222)	Unadjusted HR (95% CI)	p Value
Death	106 (9.7)	33 (3.9)	73 (31.7)	9.87 (6.49–15.0)	<0.001
Amputation	42 (4.1)	20 (2.4)	22 (10.1)	4.92 (2.68–9.03)	<0.001
Death or amputation	139 (12.9)	51 (6.1)	88 (38.5)	7.84 (5.52–11.1)	<0.001
Target limb revascularization	252 (24.3)	204 (24.9)	48 (22.0)	1.10 (0.80–1.50)	0.563
Myocardial infarction	20 (1.9)	11 (1.1)	9 (4.1)	3.75 (1.55–9.05)	0.003
ACS	48 (4.6)	36 (4.4)	12 (5.5)	1.56 (0.81–3.00)	0.182

Values are n (%).

ACS = acute coronary syndrome(s); CI = confidence interval; cTnT = cardiac troponin T; HR = hazard ratio.

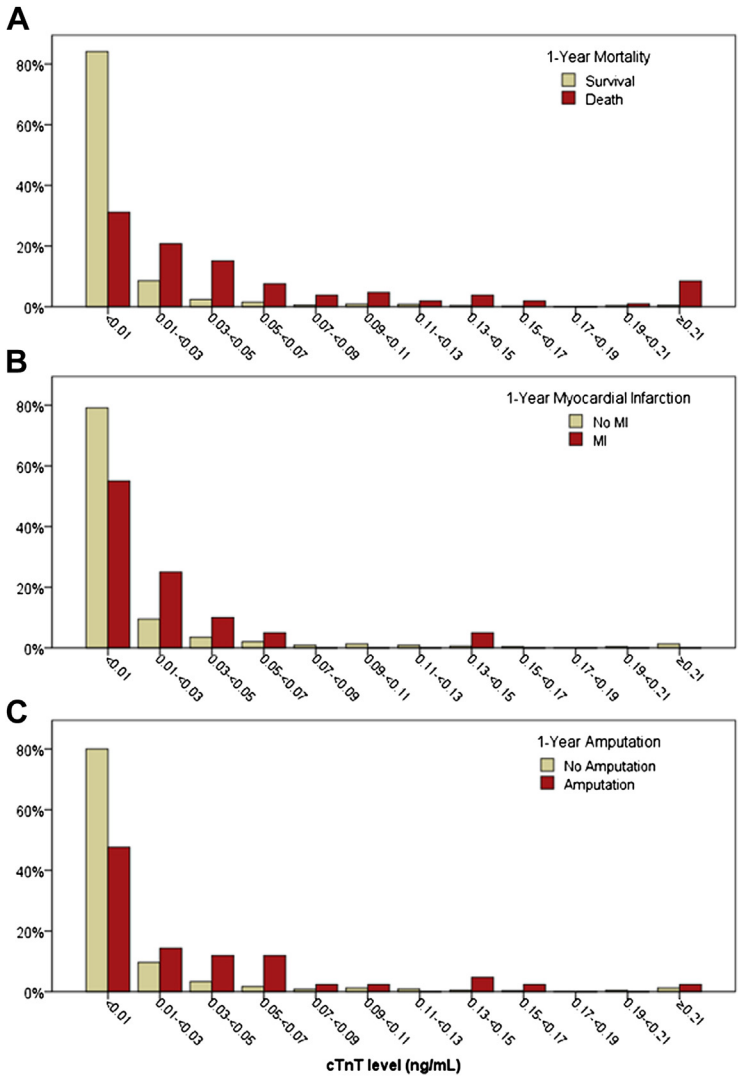

Figure 3 Cardiac Troponin T and Outcomes

The distribution of cTnT values in PAD patients according to total mortality **(A)**, myocardial infarction (MI) **(B)**, and amputation **(C)**. Abbreviations as in Figure 1.

Discussion

In this study, we examined the associations between elevated cTnT with total mortality and vascular outcomes in PAD patients who underwent an angiographic workup and a primary endovascular therapeutic approach for disease stages 2 to 5 of the Rutherford classification. Importantly, we assessed patients without clinical evidence of acute myocardial ischemia, according to the latest version of the ESC/ACCF/AHA/WHF redefinition of myocardial infarction consensus document (1). Detectable cTnT levels (≥0.01 ng/ml) were observed in 21.3% of subjects in our cohort of symptomatic PAD patients. Elevated versus normal cTnT levels, as defined by the lower limit of detection using the conventional fourth-generation cTnT assay, was associated with several established vascular risk factors (i.e., age, male sex, diabetes, and CKD) and with an increased risk of death and amputation during follow-up. Adjusting for potential confounders such as age, eGFR and the presence or absence of current smoking, diabetes, and CLI did not impair this relationship. The cutoff level of ≥0.01 ng/ml revealed an 8.1-fold (95% CI: 3.8 to 17.6) increased mortality risk and a 3.7-fold (95% CI: 1.3 to 10.3) amputation risk among PAD patients.

Conversely, the associations between cTnT concentrations and myocardial infarction were not significant in our final model after adjusting for all potential confounding factors. A similar observation has been made by Omland et al. (27), who analyzed a cohort of 3,679 patients with stable CAD. In their study, cTnT levels measured with a high-sensitivity assay were detectable in 97.7% of CAD

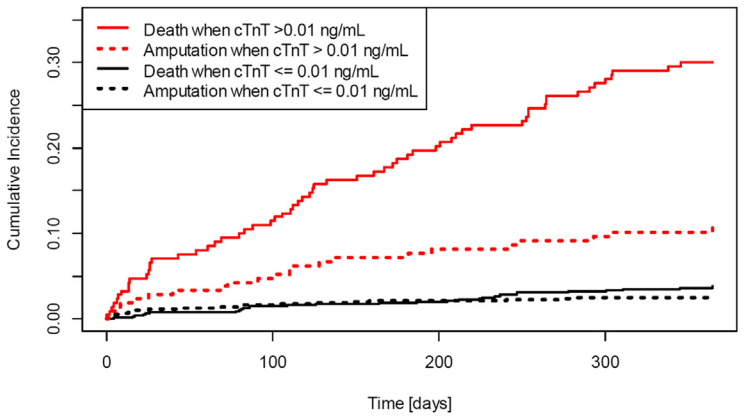

Figure 4 **Cumulative Incidence of Mortality and Amputation Stratified by cTnT Values ≥0.01 ng/ml and cTnT Values <0.01 ng/ml During 1-Year Follow-Up**

An elevated cardiac troponin T (cTnT) concentration is associated with a significantly higher mortality and amputation rate (log-rank p <0.001).

patients. Although increasing cTnT values were independently related to higher mortality and heart failure rates during a 5-year follow-up, no independent association was observed between cTnT and myocardial infarction (27). This finding is in contrast to observations in patients with ACS in whom cTnT concentrations are considered biomarkers of myocardial injury due to plaque rupture, intracoronary thrombosis, and myocardial ischemia and have been demonstrated to predict negative outcomes (2).

The plasma cTnT levels in healthy subjects are thought to result from a continuous microscopic loss of cardiomyocytes during normal life (28). There is evidence that detectable cTnT in subjects without clinical signs of acute myocardial ischemia indicates an increased risk for future cardiovascular events and unfavorable outcomes. The prevalence of cTnT values ≥0.01 ng/ml in 3,557 subjects of the population-based Dallas Heart Study was as low as 0.7% (9). That study investigated cTnT levels with a conventional fourth-generation cTnT assay, which was also used in our study. Detectable cTnT levels were typically associated with high-risk conditions, such as diabetes and advanced CKD. Moreover, elevated cTnT levels correlated with the presence of structural heart disease (e.g., left ventricular hypertrophy or dysfunction) and a subsequent risk of all-cause mortality (9,10,29).

Elevated concentrations of cardiac troponin are often observed in patients with advanced CKD, but without clinical signs of myocardial ischemia. In a large study that included 733 asymptomatic patients with ESRD, a high percentage of the patients had elevated concentrations of troponin (21). The authors of that study reported cTnT elevations in 82% of cases with a 0.01 ng/ml cutoff. In our study, elevated cTnT was prevalent in 21.3% of patients, and we also observed higher frequencies of elevated cTnT with declining renal function. Therefore, it is plausible that the association between cTnT levels and adverse outcomes is at least partly due to the presence of CKD, which by itself is indicative of an adverse outcome. However, our data reveal that cTnT levels ≥0.01 ng/ml remained an independent predictor of death and amputation even after adjusting for eGFR and other potentially confounding factors.

Only recently were cardiac troponin concentrations identified as a possible risk stratification tool in patients with acute or chronic CLI. Rittoo et al. (13) described a high prevalence of elevated cTnT among 39 patients with acute limb ischemia (44%). The cumulative survival rates after 7 days were 53% for cTnT-positive patients and 100% for cTnT-negative patients. However, the number of patients included in that study was small. A previous investigation of our study group highlighted the fact that an elevated cTnT was predictive of a worse in-hospital outcome in terms of

Table 3 **Association Between Cardiac Troponin T and Primary Outcomes Using Cox Proportional Hazards Regression Analysis**

Event	Model	Adjusted HR (95% CI)	p Value
Death	1	6.36 (3.93–10.3)	<0.001
	2	4.64 (2.82–7.64)	<0.001
	3	8.14 (3.77–17.6)	<0.001
Amputation	1	4.75 (2.34–9.65)	<0.001
	2	1.86 (0.92–3.74)	0.083
	3	3.71 (1.33–10.3)	0.012
Death or amputation	1	5.90 (3.94–8.85)	<0.001
	2	3.60 (2.39–5.43)	<0.001
	3	6.22 (3.33–11.6)	<0.001

HRs and corresponding 95% CIs are from Cox proportional hazard regression analysis. Model 1, adjustment for age and eGFR; Model 2, adjustment for age, eGFR, current smoking, diabetes, and CLI. Model 3 = Model 2 excluding patients with ECG changes suggestive of acute myocardial ischemia.

CLI = critical limb ischemia; ECG = electrocardiographic; eGFR = estimated glomerular filtration rate; other abbreviations as in Table 2.

Table 4 Prevalence of ECG Criteria Indicative of Acute Myocardial Ischemia in Patients With and Without Elevated cTnT*

Criteria	cTnT <0.01 ng/ml (n = 684)	cTnT ≥0.01 ng/ml (n = 159)	p Value
ST-segment elevation	5 (0.7%)	5 (3.1%)	0.025
ST-segment depression	60 (8.8%)	33 (20.9%)	<0.001
T-wave inversion	84 (12.3%)	48 (30.4%)	<0.001
Left bundle branch block	19 (2.9%)	8 (5.7%)	0.123

Values are n (%). *Criteria were taken from the consensus document of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction (1).
Abbreviations as in Tables 2 and 3.

mortality and amputation (HR: 3.4; 95% CI: 1.3 to 8.5) in patients with acute limb ischemia (14). Sarveswaran et al. (30) followed 152 patients with chronic CLI and without evidence of unstable CAD and discovered that elevated cardiac troponin I (cTnI) independently predicted mortality during a 2-year period (HR: 4.2; 95% CI: 1.3 to 12.7). In other investigations, Landesberg et al. (31) and Kertai et al. (32) demonstrated that low levels of asymptomatic troponin elevation during the perioperative period are associated with a poorer long-term outcome in patients undergoing major vascular surgery. To our knowledge, the present study is the first one that evaluated the prognostic value of cTnT in a large cohort of symptomatic PAD patients and provided strong evidence of an independent relationship between cTnT values ≥0.01 ng/ml and an increased mortality and amputation risk.

The mechanisms responsible for the release of cardiac troponin are most likely multifactorial and, in our patients, may include transient, clinically silent myocardial ischemia and small-vessel occlusions, myocardial strain, apoptosis of cardiomyocytes, impaired renal function, and inflammatory processes (33,34). Given the strong relationship between CAD and PAD as clinical manifestations of atherosclerosis, it is very likely that elevations in cTnT can result from transient and less-severe ischemia as a consequence of a mismatch between the oxygen supply and demand, and the exposure of myocardial cells to cytokines.

Furthermore, in the special situation of CLI, the increase in cardiac troponin appeared to be directly associated with skeletal muscle damage and rhabdomyolysis (35–37). It has been suggested that the release of necrotic muscle constituents into the circulation may have direct toxic effects on myocardial cells. However, Jaffe et al. (38) observed an increased cTnT quantified with a fourth-generation cTnT assay in 16 cases with skeletal muscle myopathy. The diagnosis of myopathy had been suggested by clinical history, examination, and increases of the creatine kinase and was confirmed by typical electromyographic changes and skeletal muscle biopsy. These results are in line with a previously published study reporting increased creatine kinase and cTnT, but not cTnI, levels among patients with idiopathic inflammatory myopathies (39). However, this issue of specificity is far from settled. There is some evidence that cTnI is also expressed in myopathic skeletal muscle tissue. Messner et al. (40) studied mRNA expression of cTnT and cTnI in the skeletal muscle and found that the mRNA of both cardiac troponin isoforms was expressed in the skeletal muscles of patients with myopathies (e.g., Duchenne muscular dystrophy). It has been suggested that re-expression of the fetal cTnT isoform in response to injury may contribute to the increase in cTnT levels (38,41). Another study investigated marathon runners and discovered cTnT to be undetectable before the race and to be elevated in 43% of the runners after the race. In this study, the elevations in cTnT were also related to higher inflammation markers (i.e., leukocyte and neutrophil counts, C-reactive protein, interleukin-6) (42).

Study limitations. The present study has some important limitations, which include the selection of patients included in this retrospective trial, the use of a conventional fourth-generation cTnT assay, and the fact that we did not perform serial cTnT testing and ECG recordings. Therefore, we cannot distinguish accurately between elevations due to acute silent myocardial ischemia and chronic disease, which is a major limitation in the interpretation of our results. However, the patients enrolled in this study were admitted to the hospital because of symptomatic PAD for angiography and endovascular revascularization, and they had no symptoms suggestive of ACS. In addition, our findings were not significantly attenuated after exclusion of patients with ECG changes that might be indicative of acute myocardial ischemia.

Previous studies have illustrated the fact that PAD patients have a substantially increased risk of cardiovascular morbidity and mortality (16,43,44). Among patients with symptomatic PAD and without clinical symptoms suggesting myocardial ischemia, an elevated cTnT is detectable in every fifth patient. According to our study, small elevations of cTnT (≥0.01 ng/ml) measured with a conventional cTnT assay predicted a markedly increased risk for death and amputation during the 1-year follow-up. A highly sensitive cTnT assay has recently been developed, allowing for the measurement of concentrations 10-fold lower than those measurable with conventional assays (45). These novel high-sensitivity cTnT assays clearly improve diagnostic performance in terms of an early and reliable diagnosis of acute myocardial infarction and have widely replaced the fourth-generation cTnT assay used in our study. However, the higher sensitivity of these novel assays is counterbalanced by a lower specificity. Thus, some of these assays allow the detection of cTnT even in up to 90% in the general population (45). Despite a number of trials providing evidence for the prognostic impact of higher hs-cTnT levels in patients with stable CAD, ACS, chronic heart failure, and ESRD (2,27,46,47), as well as in the general population (4,10,34), the optimal decision limit for the diagnosis of acute myocardial infarction and the optimal cutoff value for prognostic purposes remain to be determined (48).

Conclusions

Cardiac troponin T is frequently elevated in PAD patients and is associated with higher rates of events such as total mortality and amputation. Even small cTnT elevations predict a markedly increased risk that is independent of impaired renal function. However, further studies are needed to assess the prevalence, determinants, and prognostic implications of cTnT elevations measured by conventional or high-sensitivity assays in PAD patients.

Reprint requests and correspondence: Dr. Birgit Linnemann, JW Goethe University Hospital Frankfurt/Main, Division of Vascular Medicine, Department of Internal Medicine, Theodor-Stern-Kai 7, D-60590 Frankfurt/Main, Germany. E-mail: Birgit.Linnemann@kgu.de.

REFERENCES

1. Thygesen K, Alpert JS, White HD, on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Eur Heart J 2007;28:2525–38.
2. Lindahl B, Venge P, James S. The new high-sensitivity cardiac troponin T assay improves risk assessment in acute coronary syndromes. Am Heart J 2010;160:224–9.
3. James S, Armstrong P, Califf R, et al. Troponin T levels and risk of 30-day outcomes in patients with the acute coronary syndrome: prospective verification in the GUSTO-IV trial. Am J Med 2003;115:178–84.
4. de Filippi CR, de Lemos JA, Christenson RH, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA 2010;304:2494–502.
5. Masson S, Anand I, Favero C, et al. Serial measurement of cardiac troponin T used in a highly sensitive assay in patients with chronic heart failure. Data from 2 large randomized clinical trials. Circulation 2012;125:280–8.
6. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation 2007;116:427–33.
7. Khan NA, Hemmelgam BR, Tonelli M, Thompson CR, Levin A. Prognostic value of troponin T and I among asymptomatic patients with end-stage renal disease. A meta-analysis. Circulation 2005;112:3088–96.
8. Wang AY, Lai KN. Use of cardiac biomarkers in end-stage renal disease. J Am Soc Nephrol 2008;19:1643–52.
9. Wallace TW, Abdullah SM, Drazner MH, et al. Prevalence and determinants of troponin T elevation in the general population. Circulation 2006;113:1958–65.
10. de Lemos JA, Drazner MH, Omland T, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 2010;304:2503–12.
11. Saunders JT, Nambi V, de Lemos JA, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 2011;123:1367–76.
12. Daniels LB, Laughlin GA, Clopton P, Maisel AS, Barrett-Connor E. Minimally elevated cardiac troponin T and elevated n-terminal pro-B-type natriuretic peptide predict mortality in older adults: results from the Rancho Bernardo Study. J Am Coll Cardiol 2008;52:450–9.
13. Rittoo D, Stahnke M, Lindesay C, Grocott E, Hickey N, Downing R. Prognostic significance of raised cardiac troponin T in patients presenting with acute limb ischaemia. Eur J Vasc Endovasc Surg 2006;32:500–3.
14. Linnemann B, Sutter T, Sixt S, Rastan A, et al. Elevated cardiac troponin T contributes to prediction of worse in-hospital outcomes after endovascular therapy for acute limb ischemia. J Vasc Surg 2012;55:721–9.
15. Hafner G, Thome-Kromer B, Schaube J, et al. Cardiac troponins in serum in chronic renal failure. Clin Chem 1994;40:1790–1.
16. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg 2007;33 Suppl 1:S1–75.
17. Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. N Engl J Med 1998;339:799–805.
18. Pasqualini L, Schiaci G, Pirro M, et al. Renal dysfunction predicts long-term mortality in patients with lower extremity arterial diease. J Intern Med 2007;262:668–77.
19. Hallen J, Johansen OE, Birkeland KI, et al. Determinants and prognostic implications of cardiac troponin T measured by a sensitive assay in type 2 diabetes mellitus. Cardiovasc Diabetol 2010;9:52.
20. Irfan A, Twerenbold R, Reiter M, et al. Determinants of high-sensitivity troponin T among patients with a noncardiac cause of chest pain. Am J Med 2012;125:491–8.
21. Apple FS, Murakami MM, Pearce LA, Herzog CA. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. Circulation 2002;106:2941–5.
22. Hermsen D, Apple F, Garcia-Beltran L, et al. Results from a multicenter evaluation of the 4th generation Elecsys troponin T assay. Clin Lab 2007;53:1–9.
23. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39 Suppl 1:S1–266.
24. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Report of a WHO/IDF consultation. 14 January 2006; Available at: http://whqlibdoc.who.int/publications/2006/9241594934_eng.pdf. Accessed March 25, 2013.
25. Guidelines Subcommittee. 1999 World Health Organization-International Society of Hypertension guidelines for the management of hypertension. J Hypertens 1999;17:151–83.
26. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
27. Omland T, de Lemos JA, Sabatine MS, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med 2009;361:2538–47.
28. Tate JR. Troponin revisited 2008: assay performance. Clin Chem Lab Med 2008;46:1489–500.
29. Ammann P, Maggiorini M, Bertel O, et al. Troponin as a risk factor for mortality in critically ill patients without acute coronary syndromes. J Am Coll Cardiol 2003;41:2004–9.
30. Sarveswaran J, Ikponmwosa A, Asthana S, Spark JI. Should cardiac troponins be used as a risk stratification tool for patients with chronic critical limb ischaemia? Eur J Vasc Endovasc Surg 2007;33:703–7.
31. Landesberg G, Shatz V, Akopnik I, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. J Am Coll Cardiol 2003;42:1547–54.
32. Kertai MD, Boersma E, Klein J, Van Urk H, Bax JJ, Poldermans D. Long-term prognostic value of asymptomatic cardiac troponin T elevations in patients after major vascular surgery. Eur J Vasc Endovasc Surg 2004;28:59–66.
33. Jeremias A, Gibson CM. Narrative review: alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. Ann Intern Med 2005;142:786–91.
34. Otsuka T, Kawada T, Ibuki C, Seino Y. Association between high-sensitivity cardiac troponin T levels and the predicted cardiovascular risk in middle-aged men without overt cardiovascular disease. Am Heart J 2010;159:972–8.
35. De Gennaro L, Brunetti ND, Cuculo A, et al. Increased troponin levels in nonischemic cardiac conditions and noncardiac diseases. J Interv Cardiol 2008;21:129–39.
36. Punukollu G, Gowda RM, Khan IA, et al. Elevated serum cardiac troponin I in rhabdomyolysis. Int J Cardiol 2004;96:35–40.
37. Lavoinne A, Hue G. Serum cardiac troponin I and T in early post-traumatic rhabdomyolysis. Clin Chem 1998;44:667–8.
38. Jaffe AS, Vasile VC, Milone M, Saenger AK, Olson KN, Apple FS. Diseased skeletal muscle. A noncardiac source of increased

circulating concentrations of cardiac troponin T. J Am Coll Cardiol 2011; 58:1819–24.
39. Aggarwal R, Lebiedz-Obrobina D, Sinha A, Manadan A, Case JP. Serum cardiac troponin T, but not troponin I, is elevated in idiopathic inflammatory myopathies. J Rheumatol 2009;36: 2711–4.
40. Messner B, Baum H, Fischer P, Quasthoff S, Neumeier D. Expression of messenger RNA of the cardiac isoforms of troponin T and I in myopathic skeletal muscle. Am J Clin Pathol 2000;114: 544–9.
41. Bodor GS, Survant L, Voss EM, Smith S, Porterfield D, Apple FS. Cardiac troponin T composition in normal and regenerating human skeletal muscle. Clin Chem 1997;43:476–84.
42. Saravia SG, Knebel F, Schroeckh S, et al. Cardiac troponin T release and inflammation demonstrated in marathon runners. Clin Lab 2010; 56:51–8.
43. Diehm C, Allenberg JR, Pittrow D, et al. Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. Circulation 2009;120:2053–61.
44. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992; 326:381–6.
45. Twerenbold R, Jaffe A, Reichlin T, Reiter M, Mueller C. High-sensitive troponin T measurements: what do we gain and what are the challenges? Eur Heart J 2012;33:579–86.
46. Latini R, Masson S, Anand IS, et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation 2007;116:1242–9.
47. McGill D, Talaulikar G, Potter JM, Koerbin G, Hickman PE. Over time, high-sensitivity TnT replaces NT-proBNP as the most powerful predictor of death in patients with dialysis-dependent chronic renal failure. Clin Chim Acta 2010;411:936–9.
48. Omland T. Sensitive cardiac troponin assays: sense and sensibility. Eur Heart J 2012;33:944–6.

Key Words: amputation ■ mortality ■ peripheral arterial disease ■ troponin T.